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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/850,199	05/08/2001	Helen Fillmore	18377-0034	9734

29052 7590 03/09/2005

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 03/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/850,199	FILLMORE ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status

1. Claims 1-8 are pending.

Claims 1-8 are rejected.

2. Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Claim Rejections - 35 USC § 112

3. The rejection of claims 1-4 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al (Gene Therapy (1997) 4:1013-1022) as evidenced by Mountford et al (Human Gene Therapy (2005) 16:132-138).

Cheng teaches a plasmid DNA vector construct (see page 1014, figure 1 and page 1020, column 1 ""All the plasmids were purified and used for cell transfection as described") comprising:

a) an internal ribosomal entry site (IRES) (see page 1014, figure 1, MGIN vector with IRES element and column 2),

b) a selection marker (see page 1014, figure 1, where NEO is a selection marker in the MGIN vector),

c) a green fluorescent protein marker (see page 1014, figure 1, where EGFP is a green fluorescent protein marker).

Where the markers are transcribed as a single mRNA transcript (see page 1014, column 2, "We therefore corstructed a second retroviral vector, MGIN, in which an internal ribosome entry site (IRES) was used to coexpress the neo gene with the EGFP gene on a bicistronic transcript ernanating from the MSCV LTR (Figure 1).")

With regard to claim 2, Cheng teaches "GFP expression in MGIN transduced TF1 cells was stable since GFP-expressing TF1 cells (which were selected either by resistance to G418 or by FACS for GFP fluorescence) continued expressing EGFP at a high level for more than 2 months in the absence of G418 selection (see page 1014, column 2)." Thus, Cheng teaches stably transfected cells with the vector of claim 1.

With regard to claim 3, Cheng teaches "We report the development of a reporter system using EGFP for the analysis of conditions leading to optimal retrovirus mediated gene transfer into human primitive hematopoietic progenitors (see page 1014, column 1)". Thus, Cheng teaches stably transfection of stem cells (see page 1015, column 2).

With regard to claim 4, Cheng teaches the reagent which is the cells as discussed in claim 2. Cheng expressly uses the reagent to study biological processes (see page 1016, column 2, subheading "Effect of GFP expression on biological properties of transduced HSPC").

With regard to claim 5, Cheng teaches proteins of interest (see figure 1).

With regard to claim 6, Cheng teaches the markers are transcribed as a single mRNA transcript (see page 1014, column 2, "We therefore corstructed a second retroviral vector, MGIN, in which an internal ribosome entry site (IRES) was used to coexpress the neo gene with the EGFP gene on a bicistronic transcript ernanating from the MSCV LTR (Figure 1).")

With regard to claims 7-8, Cheng teaches the use of the MSCV LTR as the control element or promoter for expression (see figure 1, for example). This element is inherently an inducible element as demonstrated by Mountford, who teaches that MSCV can be induced by all-trans retinoic acid (see abstract). Therefore, the vector of Cheng inherently comprises an inducible promoter.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rees et al (Biotechniques (1996) 20:102-110) in view of in view of Cheng et al (Gene Therapy (1997) 4:1013-1022).

Rees teaches a plasmid bicistronic DNA vector construct (see page 104, figure 1) comprising:

a) an internal ribosomal entry site (IRES) (see page 104, figure 1),

b) a selection marker (see page 104, figure 1,where there is an NEO selectable marker under the control of the IRES element),

With regard to claims 2 and 4, Reese teaches "To facilitate the creation of stable cell lines, we have developed a bicistronic expression vector the predisposes every transfected cell to express recombinant protein and at apparently high levels (see page 102, column 3)."

With regard to claim 5, Rees teaches expression of a protein of interest, for Rees this is the human serotonin receptor (see abstract).

With regard to claim 6, Rees teaches that the vector is bicistronic and that "both the antibiotic resistance marker and the recombinant protein are under the transcriptional control of a single promoter element (see page 104, column 2)."

Rees does not teach placement of the GFP into the vector nor placement into stem cells.

Cheng teaches a DNA vector construct (see page 1014, figure 1) comprising:

a) an internal ribosomal entry site (IRES) (see page 1014, figure 1, MGIN vector with IRES element and column 2),

b) a selection marker (see page 1014, figure 1, where NEO is a selection marker in the MGIN vector),

c) a green fluorescent protein marker (see page 1014, figure 1, where EGFP is a green fluorescent protein marker).

With regard to claim 2, Cheng teaches "GFP expression in MGIN transduced TF1 cells was stable since GFP-expressing TF1 cells (which were selected either by resistance to G418 or by FACS for GFP fluorescence) continued expressing EGFP at a high level for more than 2 months in the absence of G418 selection (see page 1014, column 2)." Thus, Cheng teaches stably transfected cells with the vector of claim 1.

With regard to claim 3, Cheng teaches "We report the development of a reporter system using EGFP for the analysis of conditions leading to optimal retrovirus mediated gene transfer into human primitive hematopoietic progenitors (see page 1014, column 1)". Thus, Cheng teaches stably transfection of stem cells (see page 1015, column 2).

With regard to claim 4, Cheng teaches the reagent which is the cells as discussed in claim 2. Cheng expressly uses the reagent to study biological processes (see page 1016, column 2, subheading "Effect of GFP expression on biological properties of transduced HSPC").

With regard to claim 5, Cheng teaches proteins of interest (see figure 1).

With regard to claim 6, Cheng teaches the markers are transcribed as a single mRNA transcript (see page 1014, column 2, "We therefore corstructed a second

retroviral vector, MGIN, in which an internal ribosome entry site (IRES) was used to coexpress the neo gene with the EGFP gene on a bicistronic transcript ernanating from the MSCV LTR (Figure 1).")

With regard to claims 7-8, Cheng teaches the use of the MSCV LTR as the control element or promoter for expression (see figure 1, for example). This element is inherently an inducible element as demonstrated by Mountford, who teaches that MSCV can be induced by all-trans retinoic acid (see abstract). Therefore, the vector of Cheng inherently comprises an inducible promoter.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the Rees vector with GFP in the place of the Cheng vector for formation of stably transfected cells since Rees notes that the vector is superior to viral vectors, commenting "In contrast" (to viral vectors) "we have shown that following transfection with pCIN, every cell line characterized expresses recombinant protein and at apparently high levels. Furthermore, the use of neomycin rather than DHFR within a bicistronic mammalian expression vector should greatly increase the versatility of such vectors (see page 109, column 3)." So an ordinary practitioner, interested in a convenient method of expressing their protein of interest in a stable way in mammalian cells would have modified the vector of Cheng, which contained both Neo and EGFP to form a bicistronic vector as taught by Rees. Further motivation to place the EGFP into expression vectors is provided by Cheng, who extols the GFP as "readily detectable in many transiently transfected cells (see page 1014, column 1)." Cheng further notes that the EGFP is hundreds fold more sensitive than GFP (Cheng notes

that a previous EGFP mutant is 35 fold more sensitive and his mutant is 17 fold more sensitive than the previous mutant, so it must be 595 fold more sensitive than GFP). Motivations to modify the use of the vector of Rees, with GFP and Neo as taught by Cheng, include the teaching by Rees that such a vector will "permit the rapid and efficient production of stable mammalian cell lines for the characterization of recombinant protein, as this vector appears to predispose all transfected cells to express such protein (see abstract)." Thus, for all of these reasons, an ordinary practitioner would have been motivated to for bicistronic vectors with Neo and GFP as taught by Cheng in the IRES vector of Rees in order to permit the rapid and efficient production of stable mammalian cell lines, a goal of both Rees and Cheng.

Response to Arguments

9. Applicant's arguments filed February 18, 2005, have been fully considered but are not considered persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the

references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is provided in the rejection. The rejection notes, among other motivations that "an ordinary practitioner, interested in a convenient method of expressing their protein of interest in a stable way in mammalian cells would have modified the vector of Cheng, which contained both Neo and EGFP to form a bicistronic vector as taught by Rees." Given the express motvation discussed in the rejection, it is clear that an ordinary practitioner would have been motivated to modify the vector of Cheng to be bicistronic as discussed by Rees.

Applicant then argues that Cheng teaches away from the use of a plasmid vector because Cheng states that viral vectors are the "primary choice". First, Cheng is using a plasmid vector (see page 1020, column 1, "All the plasmids were purified and used for cell transfection as described"). However, even if Cheng solely disclosed viral vectors, a preference for one type of vector does not teach away from functional alternatives. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Cheng had a preferred embodiment, this embodiment does not prevent the use of alternative embodiments or

constitute a teaching away from such embodiments such as those suggested by the Rees reference.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
3/4/05